REMARKS

Claims 1, 3, 5-8, 11-21 and 24-45 are currently pending in this application. Claims 13-15 and 24-45 stand withdrawn as being drawn to a non-elected invention. Thus, claims 1, 3, 5-8, 11, 12 and 16-21 are under consideration. Claims 46-49 are new. Support for new claims 46-49 is found generally in the original claims and in the specification; for example, support is found in the specification at Page 4, paragraph [0059] and Page 6, paragraph [0076]. Thus, it is believed that no new matter has been entered.

Status of Application, Amendments, and/or Claims

The Examiner stated that a request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) was filed in this application after final rejection. Additionally, the Examiner stated that because the application is eligible for continued examination and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn and Applicants' submission filed on November 23, 2009 has been entered.

The Examiner also stated that claims 22 and 23 have been cancelled and claim 1 has been amended and the amendment made of record. Moreover, the Examiner stated that claims 1, 3, 5-8, 11-21, and 24-45 are pending the instant application, claims 13-15 and 24-45 stand withdrawn as being drawn to a non-elected invention, and claims 1, 3, 5-8, 11, 12, and 16-21 are under consideration.

Withdrawn Rejections

The Examiner stated that claims 22 and 23 have been cancelled, thereby rendering all rejections of these claims moot. Additionally, the Examiner stated that the rejection of claims 1, 3, 5-8, 11, 12, and 16-21 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement is withdrawn in light of Applicants' amendment to the claims. Additionally, the Examiner stated that the rejection of claims 1, 3, 5, 16, 17, 19 and 20 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. (2002 Am J. Physiol. Gastrointestinal Liver Physiol. 283: G187-G195) is withdrawn in light of Applicants' amendment to the claims.

Moreover, the Examiner stated that the rejection of claims 18 and 21 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. as applied to claims 1, 17, and 20 in view of

Vignali et al. is withdrawn in light of Applicants' amendment to the claims. The Examiner also stated that the rejection of claims 6-8 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. as applied to claim 1 in view of Blumberg et al. (1999 Current Opinion in Immunology 11:648-656) is withdrawn in light of Applicants' amendment to the claims. Finally, the Examiner stated that the rejection of claims 11 and 12 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. as applied to claim 1 in view of Bing et al. (1998 World J Gastroenterology 4:252-255) is withdrawn in light of Applicants' amendment to the claims. The Examiner also stated that new rejections are set forth below.

Rejection of Claims 1, 3, 5, 16, 17, 19, and 20 under 35 U.S.C. §103

Claims 1, 3, 5, 16, 17, 19 and 20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. (2002 Am. J. Phsiol. Gastrointestinal Liver Physiol. 282:G187-G195) in view of Hart et al. (2003 J. Clin. Gastroenterology 36:111-9).

The Examiner stated that Togawa et al. teach a method of determining the efficacy of lactoferrin treatment of animals with experimentally induced inflammatory bowel disease. More particularly, the Examiner stated that Togawa et al. disclose evaluating the efficacy of treatment by comparing levels of anti-inflammatory cytokines and pro-inflammatory cytokines in TNBS-administered rats receiving lactoferrin to levels in control animals in specimens of inflamed colon, wherein the anti-inflammatory cytokines measured were IL-4 and IL-10, wherein the pro-inflammatory cytokines measured were TNF-α, IL-1β, and IL-6, and wherein the levels of cytokines were determined by ELISA assay. Moreover, the Examiner asserted that Togawa et al. disclose that the activation of pro-inflammatory cytokines was suppressed by lactoferrin administration, while anti-inflammatory cytokines were activated by lactoferrin, thereby contributing to the anti-inflammatory effect of lactoferrin and teaching a change in levels of pro-inflammatory and anti-inflammatory cytokines in response to lactoferrin treatment.

Applicants respectfully traverse these rejections.

In general, to establish a prima facie case of obviousness, the Examiner must show, by reasoning or evidence, one or more of the following rationales: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known

element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "*Obvious to try*" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; or (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP §2143 and *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 167 L.Ed.2d 705, 82 USPQ2d 1385 (2007). The Examiner has failed to establish any of the rationales set forth above to support the conclusion of obviousness.

A rejection based on §103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. *In re Warner*, 154 USPQ 173, 178 (CCPA 1967). The Examiner may *not*, because he may doubt that the invention is patentable, resort to speculation, unfounded assumptions, or hindsight reconstruction to supply deficiencies in his required factual basis. *Id.*

Independent claim 1 recites, *inter alia*, a method of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals comprising: (a) measuring the level of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine, (b) determining the ratio of the level of the at least one anti-inflammatory cytokine to the level of the at least one pro-inflammatory cytokine, administering said treatment, (c) measuring the level of the at least one anti-inflammatory cytokine and the at least one pro-inflammatory cytokine, and (d) determining the ratio of the level of the at least one anti-inflammatory cytokine to the level of the at least one pro-inflammatory cytokine, wherein an increase in the ratio of the levels of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of said treatment is indicative of the efficacy of said treatment, and no change or a decrease in the ratio of the levels of anti-inflammatory to pro-inflammatory cytokine is indicative of lack of efficacy of said treatment.

With regard to independent claim 1, the Examiner ***admitted*** that ***neither Togawa et al. nor Hart et al. teach or suggest determining the ratio*** of the level of ***at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment***. However, the Examiner still concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment, stating that one of ordinary skill in the art would have been motivated to compute ratios as a convenient way of determining shifts in the patterns of cytokine levels. Moreover, the Examiner asserted that one would reasonably expect success because methods of measuring cytokine levels in biological samples is well known in the art, and is taught by Togawa et al. Applicants respectfully traverse the Examiner's assertions.

Firstly, Applicants submit that Togawa et al. and Hart et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics in the treatment of inflammatory diseases of the bowel by determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment. Moreover, Applicants submit that Togawa et al. and Hart et al., singularly or in combination, fail to provide any teaching, suggestion, or motivation to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Secondly, Applicants submit that determining the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic yields unexpected results with regard to determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals *in vivo*. "Rebuttal evidence may include evidence of 'secondary considerations.'" *Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467. Additionally, the MPEP provides that, "'secondary considerations,' may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results," *see* MPEP §2141, and also provides that, "[t]he evidence may be included in the specification as filed." *See* MPEP § 2141. Moreover, the MPEP provides that, "[e]vidence that the compound or composition possesses superior and unexpected

properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness." *See* MPEP §2145.

As previously discussed, independent claim 1 recites, *inter alia*, determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic, wherein an increase in the ratio of the levels of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of the treatment is indicative of the efficacy of the treatment for inflammatory diseases of the bowel. The specification of the present invention provides that, "[i]t has surprisingly been found that by increasing the ratios described herein the symptoms of inflammatory diseases of the bowel can be alleviated." (*See* Page 6, ¶ 0076). The specification of the present invention also provides that, "[w]ithout wishing to be bound by theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (*See* Page 6, ¶ 0076).

Thus, Applicants submit that the determination of a ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic yielded unexpected results with regard to determining the efficacy of a probiotic. As a result, Applicants submit that, contrary to the Examiner's assertions, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Also with regard to independent claim 1, the Examiner admitted that Togawa et al. fail to disclose a method of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals. However, the Examiner still concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a probiotic treatment, as taught by Hart et al., with the lactoferrin treatment disclosed in Togawa et al. More particularly, the Examiner stated that Hart et al. disclose the efficacy of probiotics in the maintenance of remission of ulcerative colitis and in the treatment of Crohn's disease and, as a result, it would have been obvious to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals for a method of determining the

efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. Applicants respectfully traverse the Examiner's assertions.

Firstly, Applicants submit that neither Togawa et al. nor Hart et al., either singularly or in combination, teach or suggest a method of determining the efficacy of a probiotic treatment as recited in independent claim 1. More particularly, Applicants submit that neither Togawa et al. nor Hart et al., either singularly or in combination, teach or suggest a method of determining the efficacy of a probiotic by measuring the levels of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic and determining the ratio of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Secondly, Applicants submit that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals as claimed for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. The specification of the present invention provides that, "[t]he control of inflammatory diseases is exerted at a number of levels," (*see* Page 1, ¶ 0010), and further provides that, "[t]he controlling factors include hormones, prostaglandins, reactive oxygen and nitrogen intermediates, leukotrienes and cytokines." (*See* Page 1, ¶ 0010). Moreover, the specification of the present invention provides that the very nature of inflammatory diseases of the bowel means that screening and measuring the efficacy of potential treatments in human subjects is very difficult. (*See* Page 1, ¶ 0008).

As a result, Applicants submit that determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals *in vivo* is an unpredictable art. Thus, because of the difficulties associated with determining the efficacy of potential treatments of inflammatory diseases of the bowel in an unpredictable art, Applicants further submit that it would not have been obvious to one of ordinary skill in the art to ***randomly*** substitute, without more, a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel from the teachings of Togawa et al. in view of Hart et al.

Finally with regard to independent claim 1, the Examiner admitted that neither Togawa et al. nor Hart et al. teach or suggest measuring the level of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine before and after treatment with a probiotic. However, the Examiner still concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure cytokine levels in a biological sample before and after administration of treatment to assess the efficacy of the treatment, equating this process to measuring cytokine levels in controls. Applicants respectfully traverse the Examiner's assertions.

Firstly, Applicants submit that Togawa et al. and Hart et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics in the treatment of inflammatory diseases of the bowel by determining the levels of various anti-inflammatory and pro-inflammatory cytokines before and after treatment. Moreover, Applicants submit that Togawa et al. and Hart et al. fail to provide any teaching, suggestion, or motivation to determine the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment in the absence of controls. While the Examiner asserted that determining the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment is equivalent to measuring cytokine levels in controls, Applicants submit that studying the levels of anti-inflammatory cytokines and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment are not equivalent to measuring cytokine levels in controls.

The specification of the present invention provides that, "[i]n the in vivo method, these levels are determined both before and after administration of the treatment." (*See* Page 6, ¶ 0075). The specification further provides that, "[i]n the in vitro method, the levels of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine are determined in the treatment sample, and an untreated control biological sample tested concurrently." (*See* Page 6, ¶ 0075, emphasis added). Thus, Applicants submit that determining the levels of anti-inflammatory cytokines and pro-inflammatory cytokines before and after treatment *in vivo* are not equivalent, as the specification distinguishes between determining the levels before and after treatment and determining the levels in the treatment sample and the untreated control sample. As a result, Applicants submit that it would not have been obvious to one of ordinary skill in the art to determine

the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment in the absence of controls.

Moreover, since neither Togawa et al. nor Hart et al., singularly or in combination, teach or suggest: (1) determining the ratio of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic; (2) substituting a probiotic treatment for a lactoferrin treatment; or (3) determining the levels of various anti-inflammatory and pro-inflammatory cytokines before and after treatment with a probiotic, Applicants are left with the only conclusion that the Examiner has improperly used their application as a road map through impermissible hindsight reconstruction. The motivations the Examiner provided for his asserted combination include: (1) that it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment, because one of ordinary skill in the art would have been motivated to compute ratios as a convenient way of determining shifts in the patterns of cytokine levels; (2) that it would have been obvious to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals based upon the disclosure in Hart et al. regarding the efficacy of probiotics in the maintenance of remission of ulcerative colitis and in the treatment of Crohn's disease; and (3) that it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure cytokine levels in a biological sample before and after administration of treatment to assess the efficacy of the treatment, equating this process to measuring cytokine levels in controls.

Firstly, as previously discussed, Applicants submit that due to the unexpected results yielded from the determination of the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic, it would not have been obvious to one of ordinary skill in the art to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic. Secondly, as previously discussed, Applicants submit that because of the difficulties associated with determining the efficacy of potential treatments of inflammatory diseases

of the bowel in an unpredictable art, it would not have been obvious to one of ordinary skill in the art to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel from the teachings of Togawa et al. in view of Hart et al. Finally, as previously discussed, Applicants submit that because studying the levels of anti-inflammatory cytokines and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment are not equivalent to measuring cytokine levels in controls, it would not have been obvious to one of ordinary skill in the art to determine the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment in the absence of controls.

In contrast, the specification of the present invention provides that, "[w]ithout wishing to be bound by theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (*See* Page 6, ¶ 0076). The specification also provides that the treatments may comprise probiotic compositions. (*See* Page 3, ¶ 0056). Additionally, the specification further provides that the levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine are measured. (*See* Page 5, ¶ 0073). Thus, Applicants contend that the Examiner's combination of Togawa et al. and Hart et al. is a product of impermissible hindsight reconstruction.

As set forth above, none of the references, singularly or in combination, makes a distinction, suggestion, or recognition that: (1) the ratio of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine should be determined before and after treatment with a probiotic; (2) a probiotic treatment should be substituted for a lactoferrin treatment; or (3) the levels of various anti-inflammatory and pro-inflammatory cytokines should or can be determined before and after treatment with a probiotic absent a control. Moreover, Applicants submit that determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals *in vivo* is an unpredictable art. Therefore, without more, Applicants submit that one of ordinary skill in the art would not have been taught or motivated to: (1) determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment; (2) combine a probiotic treatment with a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals; or (3) modify the disclosure of

Togawa et al. to determine cytokine levels in a biological sample before and after administration of treatment to assess the efficacy of the treatment. As a result, Applicants respectfully request the withdrawal of the rejection of claim 1 under 35 U.S.C. §103. As claims 3, 5, 16, 17, 19 and 20 depend from independent claim 1, Applicants also respectfully request the withdrawal of the rejection of these claims under 35 U.S.C. §103.

Rejection of Claims 6-8 under 35 U.S.C. §103

Claims 6-8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claim 1 in view of Blumberg et al. (1999 Current Opinion in Immunology 11:648-656).

Applicants respectfully traverse these assertions.

Claims 6-8 recite, *inter alia*, the method according to claim 1 wherein said ratio is the ratio of the level of interleukin-10 to the level of interleukin-12 (claim 6), the method according to claim 1 wherein said ratio is the ratio of the level of transforming growth factor-β to the level of interleukin-12 (claim 7), and the method according to claim 1, wherein said ratio is the ratio of the level of interleukin 10 to the level of interferon-γ (claim 8).

The Examiner rejected independent claim 1 on the basis of the teachings of Togawa et al. and Hart et al. as set forth above; additionally, the Examiner asserted that Blumberg et al. teach immune responses uniquely involved in inflammatory bowel disease pathogenesis and note the importance of balance of pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12, and anti-inflammatory cytokines such as IL-10 and TGF-β. Further, the Examiner asserted that IL-12 is a key factor in the pathogenesis of TNBS-induced colitis and induces overproduction of IFN-γ and TNF. Based on these teachings, the Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al. and substitute measurement of pro-inflammatory cytokines taught by Blumberg et al. (IFN-γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al. (TNF-α, IL-1β, and IL-6) and the anti-inflammatory cytokine taught by Blumberg et al. (TGF-β) for the anti-inflammatory cytokine taught by Togawa et al. (IL-10). Upon making this substitution, the Examiner stated

that it would have been obvious to calculate ratios as a way of monitoring changes in the balance of levels of pro- to anti-inflammatory cytokines.

Firstly, Applicants submit that Togawa et al., Hart et al., and Blumberg et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics in the treatment of inflammatory diseases of the bowel by determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment. Moreover, Applicants submit that Togawa et al., Hart et al., and Blumberg et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics by determining the specific ratios of interleukin-10 to interleukin-12, transforming growth factor-β to interleukin-12, or interleukin 10 to interferon-γ.

Secondly, as previously discussed, Applicants submit that determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals *in vivo* is an unpredictable art. As discussed above, the specification of the present invention provides that, "[t]he control of inflammatory diseases is exerted at a number of levels," (*see* Page 1, ¶ 0010), and that, "[t]he controlling factors include hormones, prostaglandins, reactive oxygen and nitrogen intermediates, leukotrienes and cytokines." (*See* Page 1, ¶ 0010). Additionally, the specification provides that, "[m]ultiple mechanisms exist by which cytokines generated at inflammatory sites influence the inflammatory response," (*see* Page 1, ¶ 0011), and further provides that "[m]ost cytokines are peleiotropic and express multiple biologically overlapping activities." (*See* Page 1, ¶ 0011). Moreover, the specification provides that, "as many cytokines may have both pro- and anti-inflammatory activities, it is very difficult to attribute disease symptoms, or recovery there from, with a particular individual cytokine." (*See* Page 1, ¶ 0011). The specification further provides that, "[w]ithout wishing to be bound by the theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (*See* Page 6, ¶ 0076).

As a result, Applicants submit that it would not have been obvious to one of ordinary skill in the art to determine the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel by determining the specific ratios of interleukin-10 to interleukin-12, of transforming growth factor-β to interleukin-12, and of interleukin 10 to the level of interferon-γ. More particularly, Applicants

submit that it would not have been obvious to one of ordinary skill in the art to modify the teachings of Togawa et al. by substituting measurement of the pro-inflammatory cytokines taught by Blumberg et al. (IFN-γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al. (TNF-α, IL-1β, and IL-6), and by substituting the anti-inflammatory cytokine taught by Blumberg et al. (TGF-β) for the anti-inflammatory cytokine taught by Togawa et al. (IL-10), wherein cytokines exhibit multiple biologically overlapping activities, wherein determining the efficacy of potential treatments in humans for inflammatory diseases of the bowel is difficult, and wherein the art is unpredictable.

Finally, Applicants submit that the Examiner's citation of Blumburg et al. fails to cure the deficiencies of Togawa et al. and Hart et al. as previously discussed. For all of these reasons, Applicants respectfully request the withdrawal of the rejection of claims 6-8 under 35 U.S.C. §103(a).

Rejection of Claims 18 and 21 under 35 U.S.C. §103

Claims 18 and 21 are rejected under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claims 1, 17 and 20 in view of Vignali et al. (cited in previous Office Action).

Applicants respectfully traverse these assertions.

The Examiner rejected independent claim 1 on the basis of the teachings of Togawa et al. and Hart et al. as set forth above. The Examiner narrowly cited Vignali et al. for teaching a method of measuring levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine in a biological sample by multiplexed ELISA's using coded microspheres coupled with a flow cytometer detection system; however, Vignali et al. fail to cure the deficiencies of Togawa et al. and Hart et al. as previously discussed. As a result, Applicants respectfully request the withdrawal of the rejection of claims 18 and 21 under 35 U.S.C. §103(a).

Rejection of Claims 11 and 12 under 35 U.S.C. §103

Claims 11 and 12 are rejected under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claim 1 in view of Bing et al. (1998 World J. Gastroenterology 4:252-255, cited in previous Office Action).

Applicants respectfully traverse these assertions.

The Examiner rejected independent claim 1 on the basis of the teachings of Togawa et al. and Hart et al. as set forth above. Bing et al. was narrowly cited for teaching measuring cytokine levels produced by peripheral blood mononuclear cells isolated from patients with IBS; however, Bing et al. fail to cure the deficiencies of Togawa et al. and Hart et al. as previously discussed. As a result, Applicants respectfully request the withdrawal of the rejection of claims 11 and 12 under 35 U.S.C. §103(a).

New Claims 46-49

New claims 46-49 have been added herein. Applicants submit that new claim 46 is allowable over Togawa et al. and Hart et al., as new claim 46 recites at least all of the limitations found in independent claim 1, which as discussed above, is believed to be allowable over Togawa et al. and Hart et al. More particularly, Applicants submit that new claim 46 is allowable over Togawa et al. and Hart et al. as new claim 46 recites the following limitations (also recited in claim 1) to which Togawa et al. and Hart et al. fail to provide any teaching, suggestion, or motivation: (1) ***determining the ratio*** of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic; (2) ***determining the efficacy of a probiotic*** as a treatment of inflammatory diseases of the bowel in mammals; and (3) ***determining the levels*** of various anti-inflammatory and pro-inflammatory cytokines should ***before and after*** treatment with a probiotic absent a control. Additionally, Applicants submit that new claim 46 is also allowable over Togawa et al. and Hart et al. as it includes an additional limitation which was not disclosed or suggested in these references.

Specifically, Applicants submit that new claim 46 is allowable over Togawa et al. and Hart et al. as it recites, *inter alia*, a method of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in humans *in vivo*. In contrast to new claim 46 which recites a method of determining the efficacy of a probiotic in humans, the disclosure of Togawa et al. is limited to the reduction of colitis in rats via the administration of lactoferrin. While Togawa et al. disclose the reduction of colitis in rats via the administration of lactoferrin, due to the unpredictable nature of the art, Applicants submit that Togawa et al. fail to teach, suggest, or motivate determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in humans *in vivo*.

For these reasons, Applicants submit that claim 46 is allowable over Togawa et al. and Hart et al. As claims 47-49 depend from allowable claim 46, Applicants submit that claims 47-49 are also in condition for allowance.

CONCLUSION

Applicants respectfully submit that the currently pending claims represent allowable subject matter. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this response. Otherwise, early notification of allowable subject matter is respectfully solicited.

Respectfully submitted,
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